

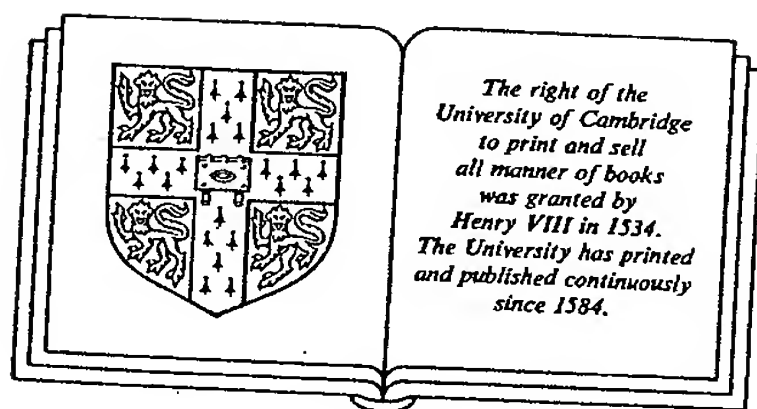
# SOME MODERN METHODS OF ORGANIC SYNTHESIS

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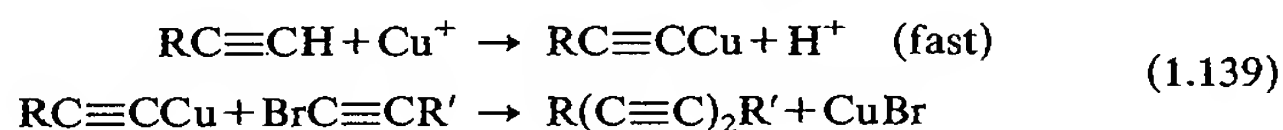
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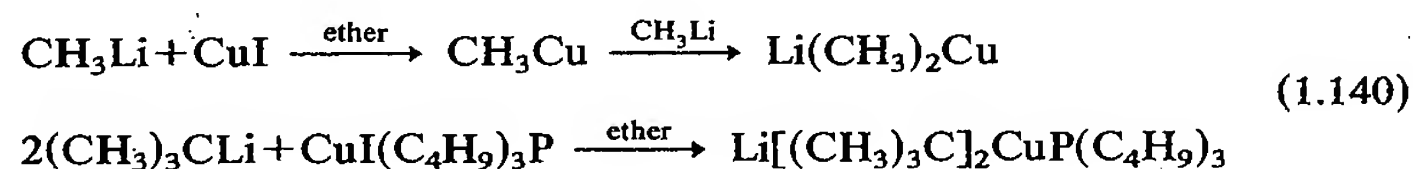
J.W.A.

The direct coupling of terminal alkynes discussed above is obviously not so well suited for the synthesis of unsymmetrical products by coupling of two different alkynes. Happily, this difficulty has been overcome by the discovery that, in presence of a base and a catalytic amount of copper(I) ion, terminal alkynes react rapidly with 1-bromo-alkynes with elimination of hydrogen bromide, to form the unsymmetrical diyne in high yield. The reaction is believed to take the course shown in (1.139). The second step regenerates the copper(I) ion which is best kept at low concentration to avoid self-coupling of the bromoalkyne. The addition of a base facilitates the reaction by removing the liberated acid and assisting in the solution of the copper(I) derivative. This valuable reaction has already been used to synthesise a variety of unsymmetrical diynes, including a number of naturally occurring polyacetylenic compounds.



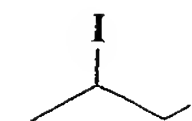
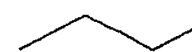
#### 1.12. Reactions of lithium organocuprates: copper-catalysed reactions of Grignard reagents

A more general procedure for coupling unlike organohalides which is not restricted to the coupling of allylic with non-allylic halides as in the reactions of  $\pi$ -allylnickel halides discussed above, makes use of the now widely employed lithium organocuprates, which are generally represented as  $\text{LiR}_2\text{Cu}$  (Posner, 1975b). These reagents are more stable and more reactive than the well-known organocopper(I) reagents (see p. 85). They are prepared *in situ* and not isolated, most conveniently by reaction of two equivalents of an organolithium compound with cuprous iodide in ether. Aryl, alkenyl and primary alkyl cuprates are readily obtained by this procedure. Secondary and tertiary alkyl cuprates are best obtained from the corresponding lithium compound and an ether-soluble derivative of copper(I) iodide such as the complex with



tributylphosphine or dimethyl sulphide. The composition of the reagent solutions is not well defined. The state of aggregation of the complexes is uncertain, but it seems likely that, in many, the organic ligands are bonded to tetrahedral clusters of four metal atoms. Recent spectroscopic studies of lithium dimethylcuprate suggest that in ether solution it exists as a dimer  $[\text{LiCu}(\text{CH}_3)_2]_2$ . These reagents undergo a variety of synthetically useful reactions (Carruthers, 1982). They are excellent reagents for

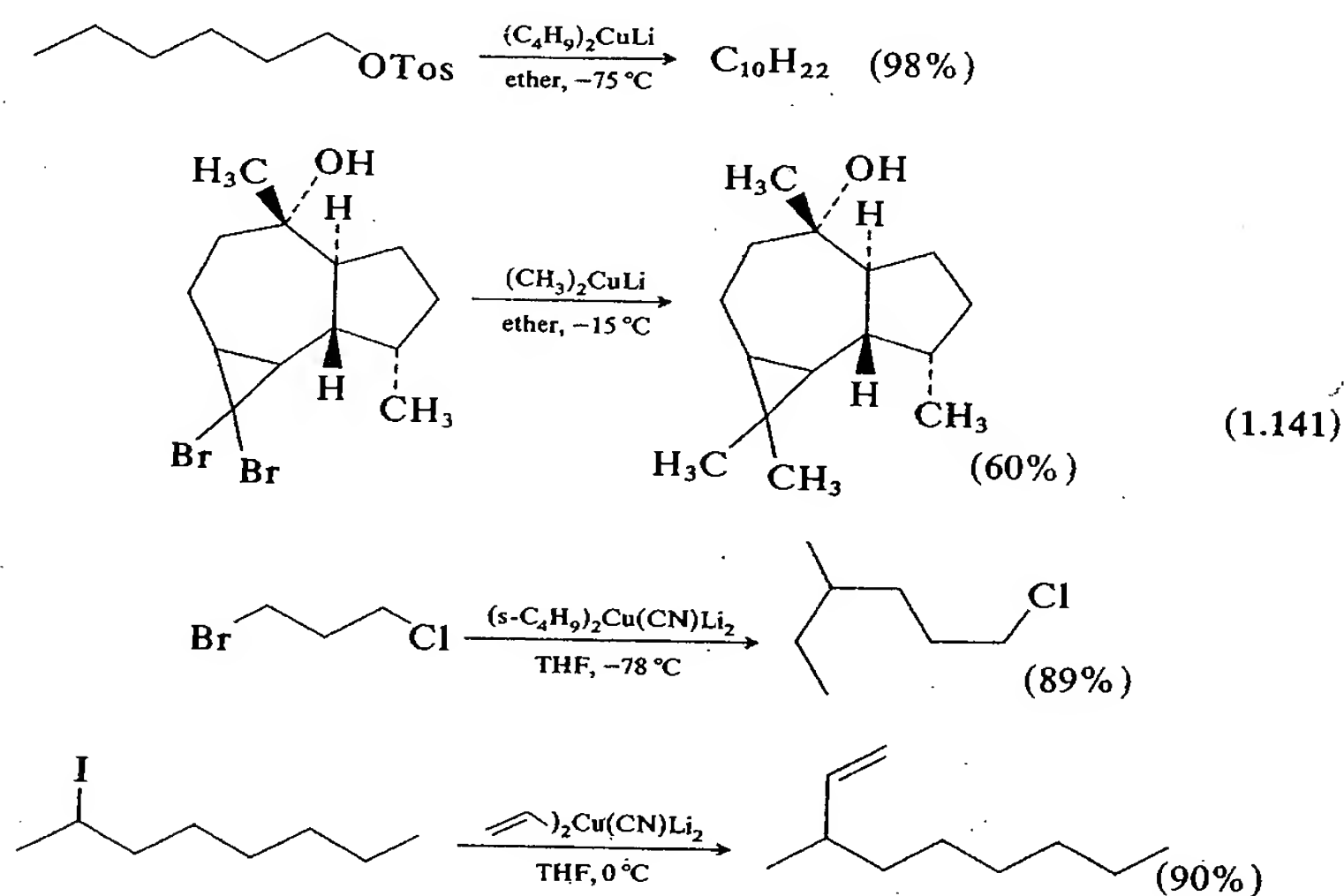
the specific alkenyl or alkyne temperature tosylates also under the conditions of an unsymmetrical diyne undergo oxidation about  $-90^\circ\text{C}$  alkyl bromide product on can be over  $\text{Li}_2\text{R}_2\text{Cu}(\text{C})$  of an organo also react give only product should be can be effective appropriate (see p. 87).



Reaction takes place and other functional halides such



the specific replacement of iodine or bromine in organic halides by alkyl, alkenyl or aryl groups. Reactions take place readily at or below room temperature to give high yields of substitution products. Primary alkyl tosylates also react very well. Ketonic carbonyl groups react only slowly under the conditions employed, so that selective reaction in the presence of an unprotected ketonic carbonyl group is possible, but aldehydes undergo ordinary carbonyl addition unless the temperature is kept below about  $-90^{\circ}\text{C}$ . Some typical reactions are shown in (1.141). Secondary alkyl bromides and iodides generally do not give very good yields of product on reaction with the ordinary cuprates  $\text{LiR}_2\text{Cu}$ , but this difficulty can be overcome by reaction with the so-called 'higher order' cuprates,  $\text{Li}_2\text{R}_2\text{Cu}(\text{CN})$ , formed *in situ* by reaction of two molecular equivalents of an organo-lithium compound with cuprous cyanide. These reagents also react very readily with primary alkyl bromides which sometimes give only poor yields with ordinary cuprates (Lipshutz *et al.*, 1983). It should be noted, however, that many of these displacement reactions can be effected just as well, or even better in certain cases, with the appropriate Grignard reagent and a catalytic amount of a copper(I) salt (see p. 87).



Reaction of lithium diphenylcuprate with (–)-(R)-2-bromobutane takes place with predominant inversion of configuration (1.142) and this and other features of the reaction of organocuprates with secondary alkyl halides suggests that they proceed by  $\text{S}_{\text{N}}2$  displacement at carbon.